I. REMARKS

Claims 1-116 are pending. Claims 1-30 and 82-116 have been withdrawn from consideration by the Office as being drawn to a non-elected invention. Claims 31-33, 48, 56 and 64-81 remain rejected under 35 U.S.C. § 103(a). All examined claims also stand rejected under 35 U.S.C. § 112, first paragraph.

Applicants traverse these rejections. For the following reasons and for the reasons of record, Applicants request that these rejections be reconsidered and withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 31-33, 48, 56 and 64-81 remain rejected under 35 U.S.C. § 103(a) as allegedly unpatentable "over Wong and Mehta, in view of Hoogenboom and Chanock." As discussed herein, this rejection is improper and should be withdrawn.

The References Cited By the Office

Applicants again request clarification from the Office as to the basis of the § 103 rejection. The MPEP clearly states "35 U.S.C. 103 authorizes a rejection where, to meet the claim, it is necessary to modify a **single** reference or combine it [the **single** reference] with one or more other references. ... It is important for an Examiner to properly communicate the basis for a rejection so that the issues can be identified early and the applicant can be given fair opportunity to reply."[1] (MPEP 706.02(j), emphasis added).

The Office has not properly identified the primary reference and the combination of references that form the basis of the 103 rejection. At first, it appears that the Office is relying on a combination of Wong and Mehta as the single primary reference, stating at

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[1]The cases (*In re Bush*, *In re Cowles*) cited by the Office in refusing to clarify this rejection do not absolve the Examiner of the responsibility of clearly informing Applicants of the issues. Nor were Applicants' previous arguments based on this request for clarification. Rather, as set forth by the MPEP, Applicants request clarification because understanding the basis of a rejection is a necessary prerequisite to making appropriate arguments.

the outset of the rejection that certain claims are unpatentable "over Wong and Mehta, in view of Hoogenboom and Chanock." (Office Action, page 2, emphasis added). Yet, in the concluding paragraph the order of cited references are reversed and the Examiner states:

> "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned and identified sequences encoding human Fab fragment specific for the E2 protein of HCV from a combinatorial library through the methods of Hoogenboom and to have further cloned these sequences into appropriate expression vectors for the purposes of recombinant expression of the Fab fragments as set forth by Chanock. Both Mehta and Wong disclose the monoclonal antibodies against E2 can be made and identified and have useful purposes."

Thus, the applied combination of references remains ambiguous and Applicants request that it be precisely laid out.

Should the Office be relying on Hoogenboom as the primary reference, Applicants again point out that this reference is completely inapplicable as it discloses only **humanized** murine antibodies and is silent as to the claimed **human** monoclonal antibodies. In addition, should the Office be relying on Chanock as the primary reference, Applicants remind the Examiner that the Federal Circuit has clearly held that references disclosing general techniques of biotechnology do not render particular molecules obvious. (see, e.g., *In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993)). Further reasons for the lack of motivation to combine these references (in any order) are discussed below.

In sum, the 103 rejection should be clarified by the Office. In the meantime, Applicants address how this rejection is improper regardless of the combination of references used.

The Basis of the 103 Rejection

As noted above, the Office has a duty to clearly set forth the basis of any § 103

rejection. Thus, in addition to clarification of how the cited references are applied, Applicants also request that the basis of the remaining 103 be rejection be more clearly set forth. Specifically, a proper 103 rejection must contain:

> "(A) the relevant teachings of the prior art relied upon, preferably with reference to the relevant column or page(s) and line number(s) where appropriate;
>
> (B) the difference or differences in the claim over the applied reference(s);
>
> (C) the proposed modification of the applied reference(s) necessary to arrive at the claimed subject matter and
>
> (D) an explanation why one of ordinary skill in the art at the time the invention as made would have ben motivated to make the proposed modification." (see, M.P.E.P. 706.02(j)).

In the pending case, the Office has not set forth the differences between claims and the references. Nor does the Action reference particular passages (*e.g.*, pages, lines numbers) that are considered relevant. Despite these shortcomings, Applicants have previously, and reiterate herein, why the combined teachings of the cited references do not render the pending claims unpatentable.

No combination of References Suggests the Claimed Invention

There is no combination of the four cited references that renders the claims unpatentable. As a threshold matter, Applicants note that they did **not** argue against the references individually in their previous response. Rather, as is necessary, Applicants summarized what each reference teaches and fairly suggests and, subsequently, explained why these references do not render the rejected claims obvious. These reasons are summarized again below.

In order to establish a *prima facie* case of obviousness the Office must show three things. First, there must be a suggestion or motivation to modify the reference or to combine the teachings of the references to arrive at the claimed invention. The courts have repeatedly held that using "hindsight reconstruction" to provide the necessary

motivation is improper. (see, e.g., *In re Fine*, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); *In re Napier* 34 USPQ2d 1782, 1784 (Fed. Cir. 1995) stating that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention absent some teaching, suggestion or incentive supporting the combination.")[2]. Moreover, the Federal Circuit has repeatedly warned that the requisite motivation must come from the prior art, not from applicant's specification. see, e.g., *In re Dow Chemical*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988).

In addition to looking to the references to determine if they suggest doing what the inventors have done, the Office must also consider if the art provides the required expectation of succeeding in that endeavor. It is insufficient for the Office to assert that the invention was "obvious to try". *In re Dow, supra.* Lastly, there must be an explanation as to why a skilled artisan would have been motivated at the time to make the proposed modification. (see, e.g., MPEP 706.02(j); *In re Sernaker*, 217 USPQ 1 (Fed. Cir. 1983)).

In the pending case, the Office has failed to meet these criteria. There is no suggestion or motiviation to modify, alone or in combination, the teachings of the references to arrive at the claimed invention -- isolated nucleic acid molecules encoding human monoclonal Fabs that exhibit specificity for the E2 protein of HCV.

Mehta and Wong are each relied upon as evidence that monoclonal antibodies to E2 existed and were "desirable" and "useful." However, neither "desirability" nor "usefuleness" are substitutes for the requisite motivation or suggestion that is entirely absent from both these references.

Mehta is relied on "as evidence that the monoclonal antibodies against E2 protein existed and had uses in immunoassay protocols at the time the invention was made."

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[2]Applicants note that the case cited by the Examiner allegedly supporting hindsight reconstruction to support an obviousness rejection is not a Federal Circuit decision. Therefore, this case is not controlling. More recent case law on this topic is cited herein.

(Office Action, page 5). The claims are not directed to any monoclonal antibodies. They are directed to nucleic acids encoding specific human Fabs. Mehta's disclosure is restricted entirely to mouse antibodies. Furthermore, Mehta does not teach isolated nucleic acid molecules encoding monoclonal Fab molecules. Indeed, the only Fab molecules discussed in Mehta are polyclonal, namely Fab dimers derived from IgG molecules purified from individuals serapositive for antibodies to HCV proteins. (Mehta, col. 11, lines 6-10). Moreover, Mehta does not teach any nucleic acid sequences for the murine monoclonal antibodies, the sequences in the sequence listing represent HCV peptide sequences (see, Mehta, Example 1 for SEQ ID NOs 1-6, and Example 6 for SEQ ID NOs 7-10). Thus, **none** of the claimed elements are suggested by Mehta.

Wong is similarly deficient. This brief Abstract deals with murine monoclonal antibodies to Hepatitis C Virus E2 envelope protein and discusses that these antibodies may be involved with blocking HCV penetration into cells (last sentence of the Abstract). There is simply no teaching or suggestion in Wong concerning an isolated nucleic acid molecule encoding a human Fab molecule that exhibits immunological binding affinity for a hepatitis C virus E2 antigen. In the absence of any motivation or suggestion regarding the claimed elements, there is no combination of these references could result in the claimed invention.

The Examiner attempts to provide the requisite motivation using two general method references, as reproduced above on page 3 of this response:

> "it would have been obvious to one of ordinary skill in the art at the time the invention was made to have cloned and identified sequences encoding human Fab fragment specific for the E2 protein of HCV from a combinatorial library through the methods of Hoogenboom and to have further cloned these sequences into appropriate expression vectors for the purposes of recombinant expression of the Fab fragments as set forth by Chanock. Both Mehta and Wong disclose the monoclonal antibodies against E2 can be made and identified and have useful purposes.One would have wanted to produce these antibodies because monoclonal antibodies against the E2 protein had been shown by Wong to prevent the penetration of HCV into target cells, and Mehta disclosed that these

antibodies would be useful in immunoassays and diagnostic procedures as a more reliable indication of HCV infection."

Wong and Mehta disclose only murine antibodies (as discussed above). Hoogenboom is a completely inapposite reference as it is concerned only with methods of making humanized antibodies. For its part, Chanock discloses general methods of making combinatorial libraries. There is no disclosure of the specific claimed molecules and no suggestion to make such HCV E2-specific molecules.

In sum, there is no suggestion in Wong, Mehta, Hoogenboom or Chanock to combine the references and, indeed, no combination would result in the claimed molecules. Accordingly, for the reasons presented above, the rejection under 35 U.S.C. §103 is inappropriate and withdrawal of the rejection is requested.

35 U.S.C. § 112, First Paragraph

Claims 31-81 are rejected under the written description requirement of 35 U.S.C. § 112, first paragraph because the specification allegedly does not describe the claimed invention throughout its scope. In particular, although the Office acknowledges that support for nucleic acid sequences is provided, it is asserted that the "generic" claims are insufficiently described.

Applicants traverse this rejection.

As a preliminary matter, Applicants request that the Examiner separately analyze each claim. This request is made because many of the claims are directed to specific nucleic acid sequences, acknowledged in the Office Action as sufficiently described by the specification. Thus, claims 34-47 and 49-63, which are directed to specific Sequence Identification Numbers, should not have been included in this rejection.

The "generic" claims are also sufficiently described by the specification. All that is required to meet the written description requirement is that the specification reasonably convey to persons skilled in the art that, as of the filing date, the inventors had possession

of the claimed subject matter. The interim guidelines, upon which the Office heavily relies in making this rejection, "do not constitute substantive rulemaking and hence do not have the force and effect of law." (Interim Guidelines, page 4). Rather, the case law establishes that the issue of whether the specification provides sufficient description is a question of fact. Since the facts of cases vary dramatically, specific holdings are of limited precedential value in supporting a written description rejection.

The consistent warnings by the Federal Circuit to limit the precedential value of a specific holding is particularly appropriate given the facts the pending application. The Examiner has cited various cases, including *Vas-Cath* and *Lilly*. The facts of these cases are very different from the facts of record in Applicants' case. *Vas-Cath* was concerned with whether drawings provided sufficient description for amended claims. For its part, *Lilly* was concerned with whether disclosure of amino acid sequence adequately described cDNAs encoding the protein. Thus, the cases cited in the Office Action are useful only for their reiteration of the standard described above -- claims are adequate described if the specification reasonably indicates to a skilled artisan that Applicants were in possession of the claimed invention. Applicants' specification satisfies this basic requirement.

The specification precisely describes and defines the claimed invention, by its physical properties and by structure. The physical properties of the claimed nucleic acid molecules (which encode human heavy and light chain Fabs that exhibit binding affinity for HCV E2) are described throughout the specification, and include, but are not limited to, general descriptions of suitable Fabs (*e.g.*, page 12-13); methods of making human Fabs (Examples); and sequences of exemplary Fabs (Figures and Seq. Ids.). Thus, the specification is no "mere wish or plan," as suggested by the Examiner on page 8, lines 1-2 of the Office Action. Rather, the specification provides all the necessary specifics to convey to one skilled in the art that Applicants were in possession of the claimed

invention. Accordingly, all of the pending claims are adequately described by the specification and withdrawal of this rejection is respectfully requested.

III. CONCLUSION

In view of the foregoing remarks and amendments, Applicants believe the claims are now in condition for allowance.

Please direct further communication regarding this application to:

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